Docket No.: CBR 3.0-017 CONT
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:	
Moo-Young et al.	
Application No.: 10/736,428	
Filed: December 15, 2003	Art Unit: 1617
For: TRANSDERMAL ADMINISTRATION OF MENT	Examiner: Kevin J. Capps

DECLARATION UNDER 37 CFR 1.131

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

1. Yun-Yen Tsong and Alfred J. Moo-Young, are the co-inventors of the above-identified pending U.S. Patent Application No. 10/736,428, filed in the U.S. Patent and Trademark Office on December 15, 2003, which is a continuation of U.S. Patent Application No. 09/154,287, filed in the U.S. Patent and Trademark Office on September 16, 1998, which claimed the benefit of U.S. Provisional Patent Application No. 60/059,301, filed in the U.S. Patent and Trademark Office on September 13, 1997.

2. Yun-Yen Tsong is presently employed by The Population Council, Inc., the assignee of Application No. 10/736,428, and have been employed by The Population Council, Inc. for the last 36 years.

3. Alfred J. Moo-Young is a citizen of the United States residing at 29 Cedar Street, Hastings-on-Hudson, New York 10706.

4. We invented the subject matter of Application No. 10/736,438, including that of claim 1 therein, and in accordance with our invention we reduced the invention to practice prior to August 21, 1997.

5. We are familiar with the prosecution of this patent application, as well as its parent applications, including official actions dated October 25, 2005 and June 29, 2006, in Application No. 10/736,428. In particular, the official actions dated October 25, 2005, and June 19, 2006, include a rejection based, at least in part, upon International Publication No. WO 97/29735 ("the '735 publication").

6. It is our understanding that the '735 publication was published on August 21, 1997, just more than one month prior to the effective filing date of our application in the U.S. Patent and Trademark Office.

7. We completed the invention of claim 1 of the pending application in the United States before the date of publication of the '735 publication; namely, before August 21, 1997, claim 1 reading as follows:

> 1. A transdermal dosage form comprising: a non-5α-reducible, 7α-modified androgen comprising 7α-methyl-19-nortestosterone and its pharmaceutically acceptable salts in a therapeutically effective amount, said androgen being dispersed within a pharmaceutically acceptable transdermal carrier, whereby said transdermal dosage form has a flux which is greater than that of testosterone in a similar formulation, said therapeutically effective amount comprising an amount of said non-5α-reducible, 7α-modified androgen sufficient to deliver between about

400 to about 1,600 micrograms of said androgen in bioavailable form over a 24-hour period.

8. In particular, prior to August 21, 1997, we were involved in the preparation of a transdermal drug delivery system for use in connection with certain non-5α-reducible, 7α-modified androgens, such as 7α-methyl-19-nortestosterone (MENT), and their application in a system which could be adhesively applied to the skin.

9. Prior to August 21, 1997, we thus invented and actually reduced to practice a transdermal delivery system for MENT which used MENT as a transdermal gel and which demonstrated that MENT had a flux which was greater than that of testosterone in a similar formulation, and which was able to deliver between about 400 to about 1600 micrograms of MENT in bioavailable form over a 24-hour period.

10. Attached hereto as Exhibit A is a seven-page document comprising the prepared handout for a meeting which took place prior to August 21, 1997, with the actual date thereof blanked out. This document includes a Table of Contents for that meeting and specific documents confirming specific testing which had been carried out and reported results therefrom.

11. The bioavailability of transdermal MENT gel formulations (2 mg MENT/g gel) were studied in rabbits. Under our direct supervision and control, three New Zealand white rabbits weighing 3.5 to 4.5 kg were used in each group. To each animal, either 0.2 grams of gel (0.4 mg of MENT) or 0.4 grams of gel (0.8 mg of MENT) was applied to 5X5 cm areas of shaved skin daily for both groups of rabbits for three days. Blood samples were taken on days 1 and 3 at 0, 1, 2, 4, 8, and 24 hours after application of the gel. The amount of MENT in the blood was

determined by radioimmunoassay, all of which is shown on page 4 of Exhibit A attached hereto, all of which was prepared prior to August 21, 1997. The results obtained are shown on pages 6 and 7 of Exhibit A, which correspond to FIGS. 15 and 14, respectively, in Patent Application No. 10/736,428.

12. The gel compositions themselves utilized a gel-based formulation which is set forth in Gel Formulation O in paragraph [0123] on page 37 of Patent Application No. 10/736,428, including 1.0 grams of methyl cellulose, 0.3 grams of carbopol, 0.90 grams of benzyl alcohol, 35.0 grams of propylene glycol, 10.0 grams of isopropyl alcohol, and the rest of the 100 gram composition as water.

13. The results of rat skin flux rate comparison between the use of 7α-methyl-19-nortestosterone and testosterone is shown in FIG. 9 of Patent Application No. 10/736,428, demonstrating a much higher flux rate for the 7α-methyl-19-nortestosterone than for the testosterone in the Gel Formulation O.

14. We have recently recalculated these results in terms of $\mu g/cm^2/hr$ instead of μg/ml, as shown in the figure on page 5 of Exhibit A, and these results are shown in the figure which is attached hereto as Exhibit B.

We hereby declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may

jeopardize the validity of the application or any patent issuing thereon.

Dated: February 27, 2007

By _____
YUN-YEN TSONG, Ph.D.

Dated:
March 22, 2007

By _____
ALFRED MOO-YOUNG, Ph.D.

739144_1.DOC

INTERNATIONAL COMMITTEE FOR CONTRACEPTION RESEARCH
New York,
68th Meeting

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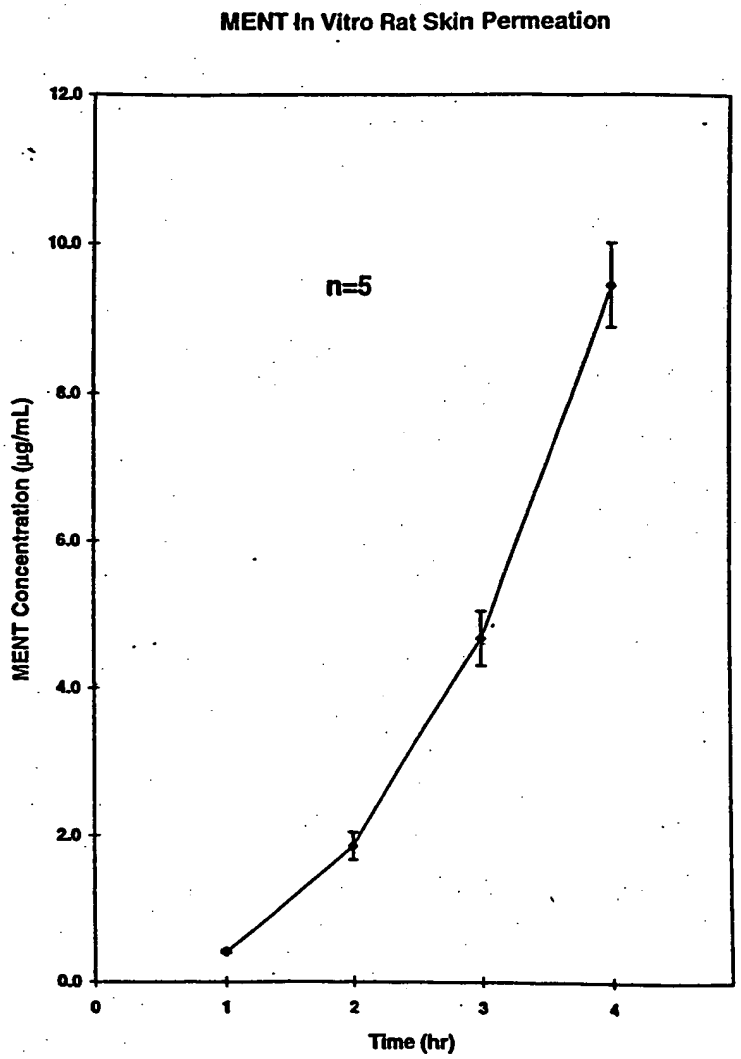
E. Transdermal Delivery of MENT

Animal Study

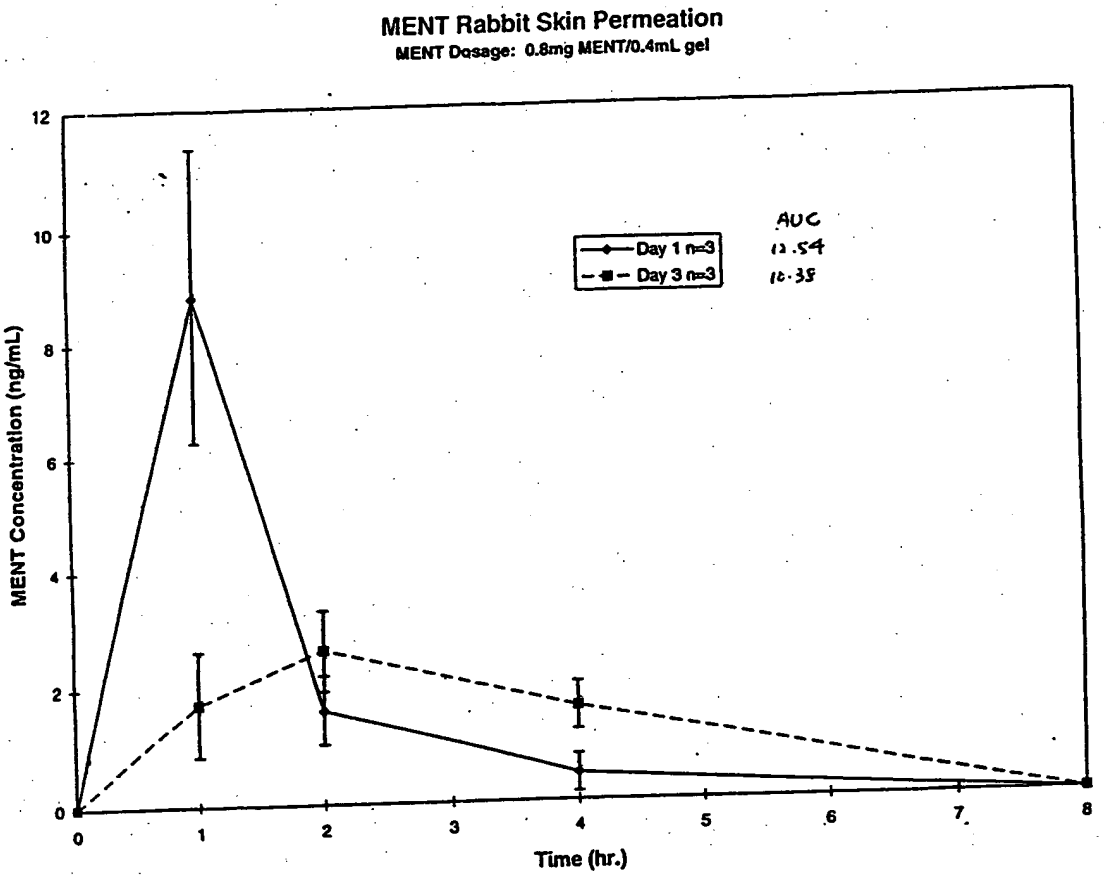
Dr. Tsong reported that MENT permeated rat skin when it was applied as a transdermal gel in the *in vitro* Franz cell study (Figure 1), though MENT acetate did not. Under the same study conditions, the rate of permeation of MENT is about three times that of Nestorone™ progestin. The bioavailability of MENT transdermal gel in rabbits was studied in collaboration with Dr. Sundaram's laboratory. Animals were divided into two groups, three rabbits per group. To one group of rabbits, 0.2 g of gel (0.4 mg MENT) was applied to a 5 x 5 cm area of shaved skin. The second group of rabbits received a double dose (0.8 mg) of MENT by applying 0.2 g of gel to each of two 5 x 5 cm patches of shaved skin. The gel was applied daily to both groups of rabbits for three days. Blood samples were taken on Days 1 and 3 at 0, 1, 2, 4, 8, and 24 hours after application of the gel. The amount of MENT in the blood was determined by radioimmunoassay. In both the high-dose (Figure 2) and low-dose (Figure 3) groups, serum levels of MENT reached a peak one hour after application of the gel on Day 1. On Day 3, MENT levels peaked two hours after application and were non-detectable after 8 hours. Calculation of the areas under the curves showed similar values for Days 1 and 3. The results indicated that transdermal delivery is a viable method of MENT administration.

Figure 1



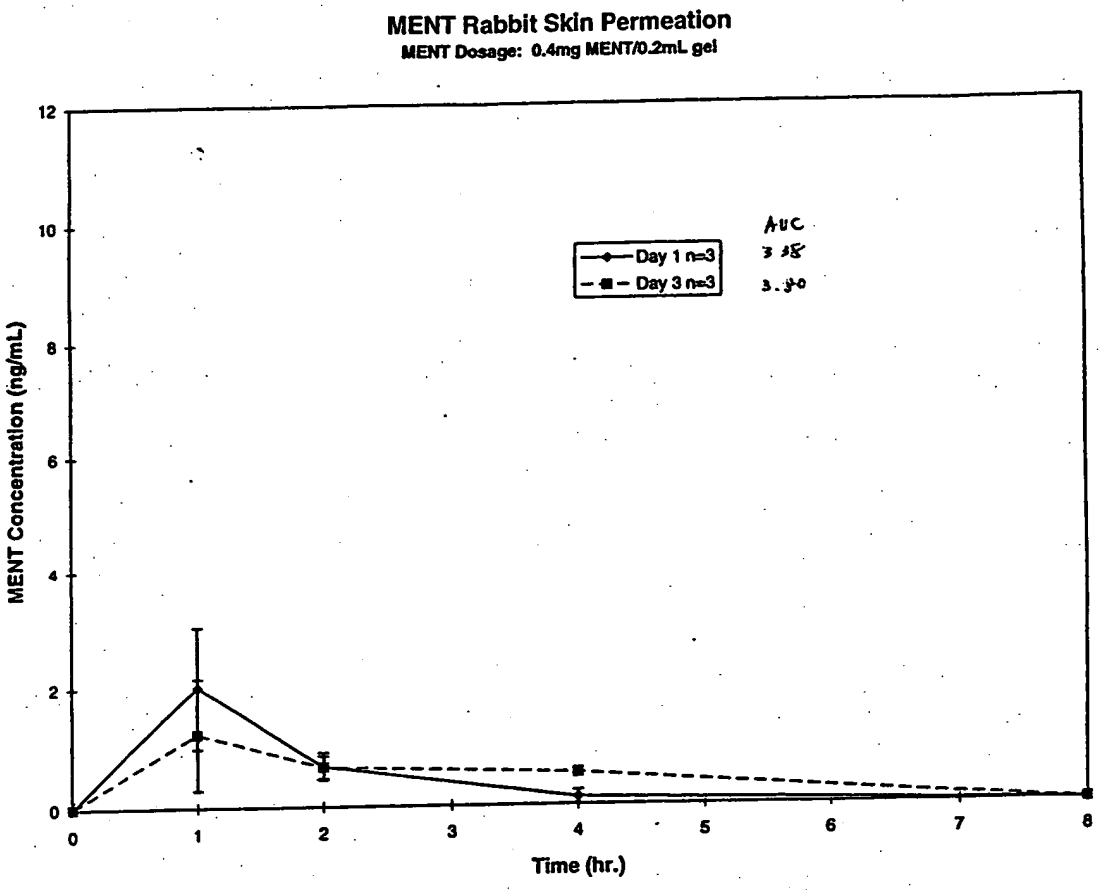
The *in vitro* rat skin permeation study of MENT transdermal gel. The gel contained 2 mg MENT per g gel

Figure 2



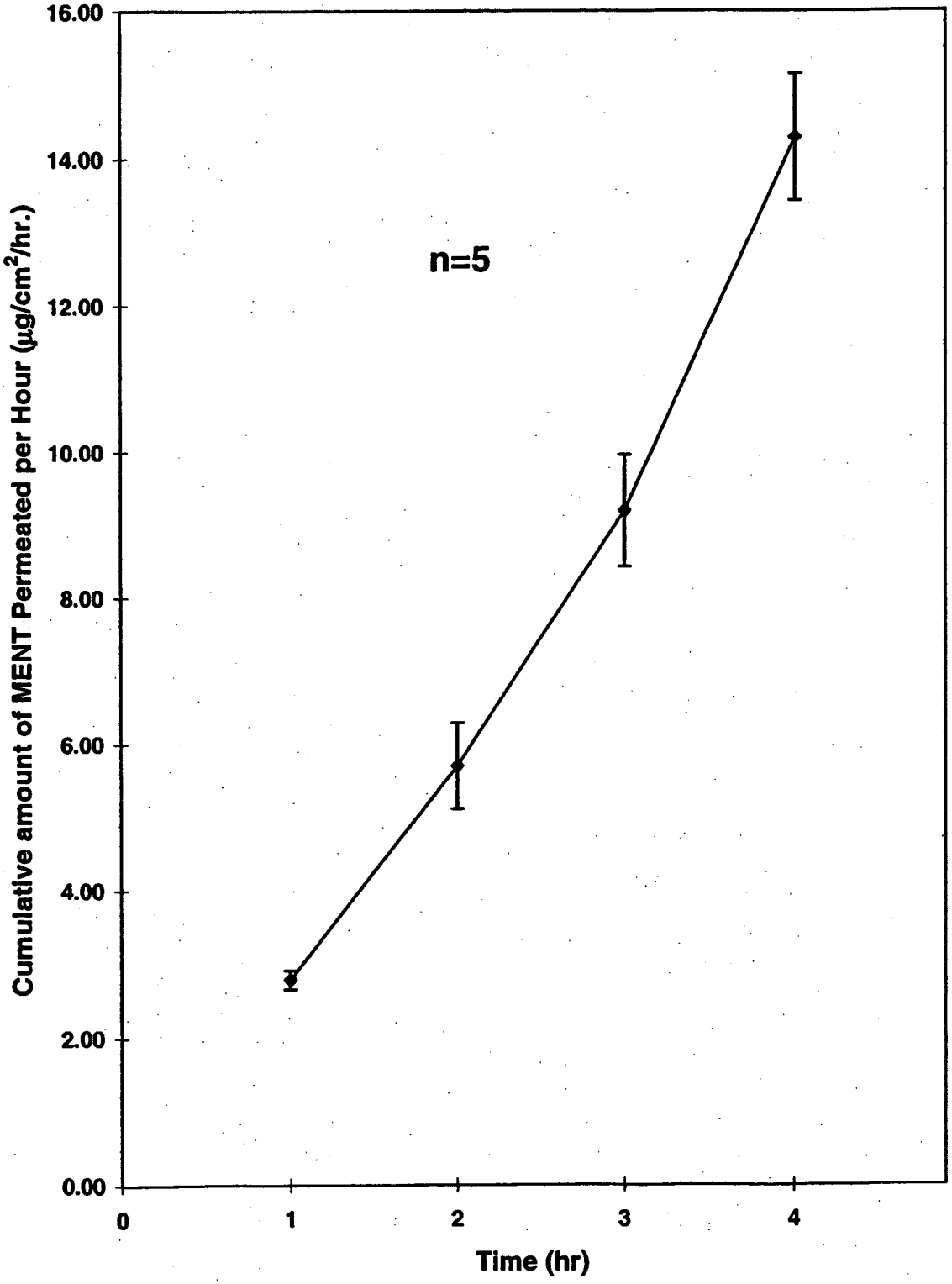
The bioavialability of MENT in rabbits after administration of 0.4 g of MENT transdermal gel (2 mg MENT per g gel) for three consecutive days.

Figure 3



The bioavialability of MENT in rabbits after administration of 0.2 g of MENT transdermal gel (2 mg MENT per g gel) for three consecutive days.

MENT In Vitro Rat Skin Permeation



MENT In Vitro Rat Skin Permeation